Angiopoietin-2: An Attractive Target for Improved Antiangiogenic Tumor Therapy
Damien Gerald, Sudhakar Chintharlapalli, Hellmut G. Augustin, and Laura E. Benjamin

Ion Channels and Transporters in Cancer: Pathophysiology, Regulation, and Clinical Potential
Stine F. Pedersen and Christian Stock

G-protein Inactivator RGS6 Mediates Myocardial Cell Apoptosis and Cardiomyopathy Caused By Doxorubicin
Juanqi Yang, Biswanath Maity, Jie Huang, Zhan Gao, Adele Stewart, Robert M. Weiss, Mark E. Anderson, and Rory A. Fisher

Trp53 Inactivation in the Tumor Microenvironment Promotes Tumor Progression by Expanding the Immunosuppressive Lymphoid-like Stromal Network
Gang Guo, Luis Marrero, Paulo Rodriguez, Luis Del Valle, Augusto Ochoa, and Yan Cui

Phase I Trial of Recombinant Modified Vaccinia Ankara Encoding Epstein–Barr Viral Tumor Antigens in Nasopharyngeal Carcinoma Patients

Earlier Detection of Breast Cancer with Ultrasound Molecular Imaging in a Transgenic Mouse Model
Sanitha V. Bachawal, Kristin C. Jensen, Amelie M. Lutz, Sanjiv S. Gambhir, Francois Tranquart, Lu Tian, and Jürgen K. Willmann

Collections of Simultaneously Altered Genes as Biomarkers of Cancer Cell Drug Response
David L. Masica and Rachel Karchin

Therapeutic Efficacy of Bifunctional siRNA Combining TGF-β1 Silencing with RIG-I Activation in Pancreatic Cancer
Jonathan Ellermeier, Jiwu Wei, Peter Duewell, Sabine Hoves, Mareike R. Stieg, Tina Adunka, Daniel Noerenberg, Hans-Joachim Anders, Doris Mayr, Hendrik Poeck, Gunther Hartmann, Stefan Endres, and Max Schnurr
LOX-Mediated Collagen Crosslinking Is Responsible for Fibrosis-Enhanced Metastasis

Thomas R. Cox, Demelza Bird, Ann-Marie Baker, Holly E. Barker, Melissa W-Y. Ho, Georgina Lang, and Janine T. Erler

Précis: The fibrotic status of a metastatic niche that is determined by the extracellular matrix plays a pivotal role in determining colonization of new sites by circulating tumor cells.

Evidence for a Role of the PD-1:PD-L1 Pathway in Immune Resistance of HPV-Associated Head and Neck Squamous Cell Carcinoma


Précis: HPV-associated oropharyngeal cancers, which are increasing in incidence in the developed world, evade immune surveillance through an escape pathway that is actively being targeted in clinical trials.

IFN-γ-Mediated Downregulation of LXA4 Is Necessary for the Maintenance of Nonresolving Inflammation and Papilloma Persistence

Chunhui Wang, Mingjie Xiao, Xiaoman Liu, Chen Ni, Jianhong Liu, Ulrike Erben, and Zhihai Qin

Précis: By helping resolve an inflammatory response, IFNγ blockade can promote tumor regression by reprogramming the inflammatory microenvironment.

Myeloid-Specific Expression of Ron Receptor Kinase Promotes Prostate Tumor Growth

Devikala Gurusamy, Jerilyn K. Gray, Peterson Pathrose, Rishikesh M. Kulkarni, Fred D. Finkleman, and Susan E. Waltz

Précis: This study suggests a new strategy to treat prostate tumors, by blocking a tyrosine kinase that supports tumor-associated macrophages that drive immune escape.

HLA-Restricted CTL That Are Specific for the Immune Checkpoint Ligand PD-L1 Occur with High Frequency in Cancer Patients

Shamaila Munir, Gitte Holmen Andersen, Özcan Met, Marco Donia, Thomas Mørch Frøsig, Stine Kiaer Larsen, Tobias Hirendfeldt Klausen, Inge Marie Svane, and Anirban Maitra

Précis: PD-L1-specific cytotoxic T cells described for the first time in this study may be useful to harness for cancer immunotherapy to defeat mechanisms of immune escape used in various cancers mediated by the PD1 pathway.

A Chimeric Receptor with NKG2D Specificity Enhances Natural Killer Cell Activation and Killing of Tumor Cells

Yu-Hsiang Chang, John Connolly, Noriko Shimasaki, Kousaku Mimura, Koji Kono, and Dario Campana

Précis: Findings illustrate how to increase the antitumor efficacy of NK cell therapy, a strategy that may be used to fight nearly any kind of human cancer.

MOLECULAR AND CELLULAR PATHOBIOLOGY

Transcription Factor Y11 Contributes to Tumor Growth by Stabilizing Hypoxia Factor HIF-1α in a p53-Independent Manner

Shourong Wu, Vivi Kasim, Mitsunobu R. Kano, Sayaka Tanaka, Shinzuke Ohba, Yutaka Miura, Kanjiro Miyata, Xueying Liu, Ako Matsuhashi, Ung-il Chung, Li Yang, Kazunori Kataoka, Nobuhiro Nishiyama, and Makoto Miyagishi

Précis: Findings suggest a mechanistic strategy to block a core hypoxia-driven progression pathway regardless of p53 status.

Arkadia Regulates Tumor Metastasis by Modulation of the TGF-β Pathway

Marco A. Briones-Orta, Laurence Levy, Chris D. Madsen, Debi-priya Das, Yigit Erker, Erik Sahai, and Caroline S. Hill

Précis: An E3 ubiquitin ligase in the TGF-β signaling pathway is not required to regulate tumor growth but to colonize metastasis sites, suggesting novel antitumor strategies.

Phosphorylation of Ribosomal Protein S6 Attenuates DNA Damage and Tumor Suppression during Development of Pancreatic Cancer

Abed Khalaileh, Avigail Dreazen, Areej Khatib, Roy Apel, Avital Swisa, Norma Kiedess-Bassir, Anirban Maitra, Oded Meyuhas, Yuval Dor, and Gideon Zamir

Précis: Findings reveal that a key mTOR effector molecule is crucial for initiation of K-Ras-induced pancreatic cancers, illuminating the centrality of this mTOR pathway to evade p53-mediated tumor suppression in this setting.
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Mixed Lineage Kinase MLK4 Is Activated in Colorectal Cancers Where It Synergistically Cooperates with Activated RAS Signaling in Driving Tumorigenesis
Miriam Martini, Mariangela Russo, Simona Lamba, Elisa Viteli, Emily Hannah Crowley, Francesco Sassi, Davide Romanelli, Milo Frattini, Antonio Marchetti, and Alberto Bardelli

Precis: Findings support the development of small molecule inhibitors of the kinase MLK4 to treat the significant number of KRAS-mutant colorectal cancers that arise in humans.

A Novel Inhibitor of STAT3 Homodimerization Selectively Suppresses STAT3 Activity and Malignant Transformation
Xiaolei Zhang, Ying Sun, Roberta Pireddu, Hua Yang, Muradi K. Uslan, Harshani R. Lawrence, Wayne C. Guida, Nicholas J. Lawrence, and Said M. Sebti

Precis: STAT3 provides critical support in cancer cells and the immune microenvironment in tumors, but bioactive small molecule inhibitors that offer tractable qualities for clinical translation have been elusive.

Alkaline Phosphatase ALPPL-2 Is a Novel Pancreatic Carcinoma-Associated Protein
Pooja Dua, Hye Suk Kang, Seung-Mo Hong, Ming-Sound Tsao, Soyoun Kim, and Dong-ki Lee

Precis: An aptamer selection strategy identifies an enzyme that may be useful for blood-based detection of pancreatic cancer.

mTOR Complex 2 Is Involved in Regulation of Chl-Dependent c-FLIP Degradation and Sensitivity of TRAIL-Induced Apoptosis
Liqun Zhao, Ping Yue, Fadlo R. Khuri, and Shi-Yong Sun

Precis: Findings show how mTORC2 stabilizes the FLIP apoptotic regulators, thereby connecting mTORC2 signaling to death receptor-mediated apoptosis.

Phenotypic Profiling of DPYD Variations Relevant to 5-Fluourouracil Sensitivity Using Real-time Cellular Analysis and In Vitro Measurement of Enzyme Activity
Steven M. Offer, Natalie J. Wegner, Croix Fossum, Kangsheng Wang, and Robert B. Diasio

Precis: An understanding of the contribution of DPYD alleles to 5-FU toxicity will facilitate the generation of clinically relevant predictive tests and promote the individualization of treatment based on genotype.

Involvement of Lyn and the Atypical Kinase SgK269/PEAK1 in a Basal Breast Cancer Signaling Pathway

Precis: This study addresses a rationale to target basal breast cancers, also known as triple negative breast cancers, which present a major clinical challenge due to their aggressive nature and lack of targeted treatments.

FOX2 Expression Links Epithelial–Mesenchymal Transition and Stem Cell Properties in Breast Cancer
Brett G. Hollier, Agata A. Tinnirello, Steven J. Werden, Kurt W. Evans, Joseph H. Taube, Tapasree Roy Sarkar, Nathalie Sphyris, Maryam Shariati, Sreedevi V. Kumar, Venkata L. Battula, Jason I. Herschkowitz, Rudy Guerra, Jeffrey T. Chang, Naoyuki Miura, Jeffrey M. Rosen, and Sendural A. Mani

Precis: Findings of this study suggest a rational new target for anti-EMT therapy of cancer stem cells, perhaps relevant to many types of malignancy.

Characterization of a Novel PERK Kinase Inhibitor with Anti-tumor and Antiangiogenic Activity
Charity Atkins, Qi Liu, Elisabeth Minthorn, Shu-Yun Zhang, David J. Figueroa, Katherine Moss, Thomas B. Stanley, Brent Sanders, Aaron Goetz, Nathan Gaul, Anthony E. Choudhry, Hasan Alsaid, Beat M. Jucker, Jeffrey M. Axtens, and Rakesh Kumar

Precis: Inhibition of PERK kinase, which controls the unfolded protein response (UPR), a near universally elevated process in cancer cells, was also found unexpectedly to affect amino acid metabolism, blood vessel density, and vascular perfusion in tumors.

Genetic Amplification of the NOTCH Modulator LNX2 Upregulates the WNT/β-Catenin Pathway in Colorectal Cancer
Jordi Camps, Jason J. Pitt, Georg Emons, Amanda B. Hummon, Channelle M. Case, Mariam Grade, Tamara L. Jones, Quang T. Nguyen, B. Michael Ghiadini, Tim Beissbarth, Michael J. Dilllipantionio, Natasha J. Caplen, and Thomas Ried

Precis: Notch and Wnt signaling pathways are upregulated by overexpression of a ligand for the endocytic adaptor protein Numb, a Notch inhibitory protein, coordinately stimulating both of these critical oncogenic pathways in colorectal cancer.

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ABOUT THE COVER

Inactivation of the tumor suppressor p53 frequently occurs in tumors and tumor-associated stromal cells. This study shows that p53 dysfunction in tumor-associated stroma of B16F1 melanoma favors tumor establishment and progression by promoting an inflammatory microenvironment. Using immunofluorescence, it was found that lymphoid-like fibroblastic reticular cells, which express ER-TR7 (green), GP38 (red), and a-SMA (blue), were markedly expanded in the tumor microenvironment lacking functional p53. The expansion of this specialized stromal network was associated with augmented myeloid derived suppressor cells and angiogenesis. For details, see the article by Guo and colleagues on page 1668.